# Antiglomerular basement membrane disease with normal renal function

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## CASE PRESENTATION

A 23-year-old man was referred to Peking University First Hospital with a 4-month history of intermittent hemoptysis. One month before admission, he experienced severe hemoptysis with cough and respiratory distress. His hemoglobin was 71.0 g/l, urinalysis revealed protein 1+, and red blood cells 3–5/high-power field (HPF). Arterial blood gas analysis showed pH 7.385, $PO_2$ 58 mm Hg, $PCO_2$ 40 mm Hg, and $SaO_2$ 88%. Chest radiograph showed diffusely parenchymal shadows in both lungs. He was diagnosed as having a pulmonary infection with respiratory failure type I and was treated with ceftazidime and erythromycin, but no improvement was obtained after 3 weeks. One week before admission, an anti-glomerular basement membrane (GBM) antibody was detected positive by enzyme-linked immunosorbent assay (ELISA) using purified bovine α(IV)NC1 as solid-phase antigen. He was then referred to our hospital.

The patient was a car repairman with a 5-year exposure to gasoline and diesel. He smoked 1–2 packs of cigarettes per day for 4 years.

Physical examination revealed a well-nourished man with no edema or rash. The temperature was 36.8°C, blood pressure 130/85 mm Hg, and pulse 90/min. The heart rate and rhythm was regular. Moist rales could be heard in both lungs. The abdomen was soft and non-tender without organomegaly.

Laboratory data on admission were as follows: white blood cells $12.8 \times 10^9$/l (normal range, 3.5–9.5 $\times 10^9$/l), hemoglobin 62.0 g/l (137–179 g/l), platelet $178 \times 10^9$/l (100–300 $\times 10^9$/l). Hepatic function was normal. Serum creatinine was 94.0 μmol/l (44–133 μmol/l) and blood urea nitrogen was 6.3 mmol/l (1.8–7.1 mmol/l). Electrolytes were in the normal range. Serum albumin was 39.6 g/l (35–50 g/l). Urinalysis revealed red blood cells 3–5/HPF (0–3/HPF) and dysmorphic red cells and the 24-h urine protein was 0.87 g (<0.15 g/24 h). Erythrocyte sedimentation rate was 14 mm/1 h (<15 mm/1 h). C-reactive protein, rheumatoid factor, antineutrophil cytoplasmic antibodies, and antinuclear antibodies were all negative. Anti-GBM antibodies were positive at 23% tested by ELISA as described above (normal range, <13%), with a titer of 1:400.

Although there was a broad differential, including small vessel vasculitis, systemic lupus erythematosus, pulmonary infection, tuberculosis, and heart failure, the clinical presentation and the laboratory workup were most compatible with a diagnosis of anti-GBM disease with Goodpasture's syndrome. After admission, a renal biopsy was performed.

## RENAL BIOPSY FINDINGS

On light microscopy, the patient had 12 glomeruli with no crescent formation. The glomeruli showed mild proliferation of mesangial cells (Figure 1). Immunofluorescence showed linear staining of IgG++ and C3++ along GBM (Figure 2). Serum anti-GBM antibodies were further confirmed by Western blot analysis using purified human α(IV)NC1 as antigen (Figure 3). The antigen specificity was identified by ELISA using recombinant human α3(IV)NC1 as solid-phase antigen. The IgG subclasses of the antibodies were restricted to IgG4.

## CLINICAL FOLLOW-UP

The patient was treated with prednisone 1 mg/kg/day for 8 weeks, with gradual tapering off within 6 months. Carbon monoxide transfer factor, arterial blood gas analysis, chest radiography, serum creatinine, and urinalysis were performed every 2 days. Under such a rigorous monitoring for lung hemorrhage and renal function, no plasmapheresis or cyclophosphamide was given to the patient. After 2 weeks, his hemoptysis stopped, and hematuria and proteinuria disappeared simultaneously. Six weeks after commencing the

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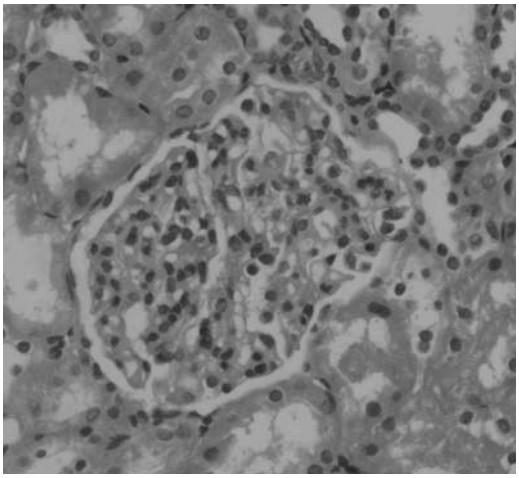

**Figure 1 | Light microscopic examination revealed mild mesangial proliferative glomerular nephritis ( × 200).**

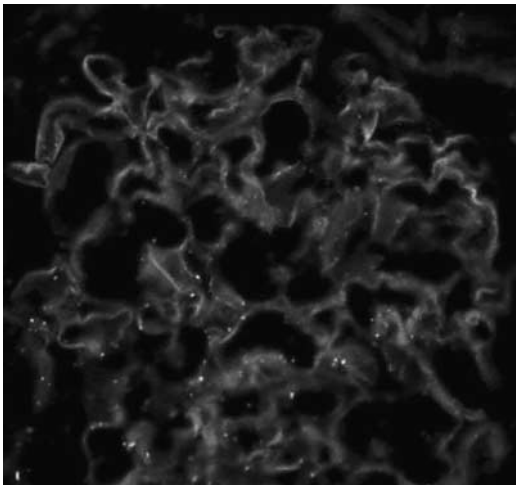

**Figure 2 | Immunofluorescence revealed linear staining of IgG along GBM ( × 400).**

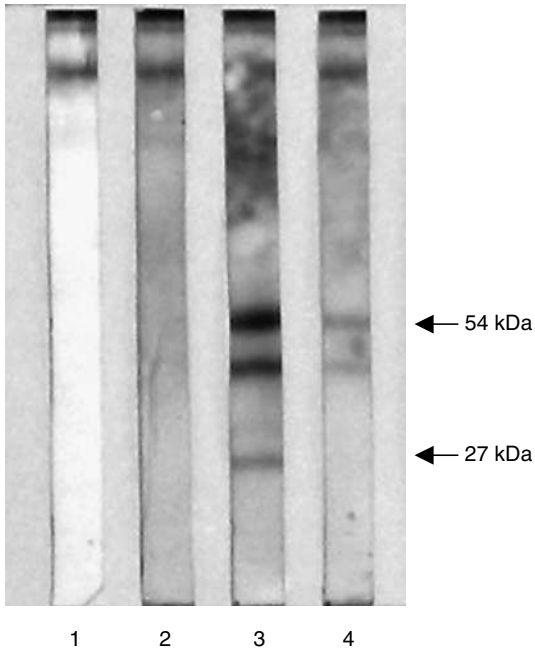


**Figure 3 | Western blot analysis using purified human α(IV)NC1 as antigen.** Lane (1) blank control; lane (2) sera from a healthy blood donor as negative control; lane (3) sera from a known patient with Goodpasture's syndrome with severe renal damage as positive control; lane (4) sera from the current patient.

treatment, his serum anti-GBM antibodies became negative. After discharge, the patient has been followed up for 7 years. His serum creatinine is 80–100 μmol/l and urine examination is normal. No relapse of hemorrhage, hematuria, or proteinuria has been observed.

## DISCUSSION

Anti-GBM disease is characterized by the formation and deposition of antibodies on the basement membranes of glomeruli and alveoli.[1] Most patients present with both alveolar hemorrhage and renal involvement. Collectively, this syndrome is known as the classic form Goodpasture's syndrome, and is frequently accompanied by extensive and rapidly progressive glomerulonephritis. The introduction of combined therapy with immunosuppressive agents and plasmapheresis has improved the prognosis of this disease.[2] However, Goodpasture's syndrome continues to be associated with a high mortality of 11%, and high morbidity, where 40% of patients might expect to become dialysis-dependent.[1,3] Over the past several years, a subgroup of patients with only minimal evidence of renal dysfunction had been described largely because of improved immunodiagnostic procedures. These patients provide valuable insights into the pathogenesis of anti-GBM disease.

### The clinical and pathological characteristics of anti-GBM disease with normal renal function

This subgroup of patients with anti-GBM disease and normal renal function usually present mainly with lung hemorrhage, which ranges from some blood streaks in the sputum to extensive hemoptysis and respiratory failure requiring intubation and mechanical ventilation. The urinary sediment examination had been reported as normal in occasional patients,[4–6] but for the most part demonstrated the presence of hematuria and proteinuria.[7–12] Macroscopic hematuria and hypertension are rare in these patients.[11] However, a moderate to severe anemia could be a symptomatic cue to the consideration of this disease.[4–6,8,10,11] Systemic symptoms (malaise, fever, or weight loss) are less common in these patients compared with those with renal impairment. These symptoms might be from the consequence of inflammation associated with glomerulonephritis, or be the symptoms of renal failure. Renal pathological examination generally reveals a mild mesangial proliferative glomerulonephritis. In some cases, a few cellular crescents may also be observed, but usually less than 50% of total glomeruli.[9] In general,

these patients have an excellent prognosis compared with the classic Goodpasture's syndrome. Indeed, renal function is preserved in the majority of patients, although a slow progression to renal failure had been observed in some. The clinical presentation of patients with anti-GBM disease and normal renal function is variable (similar to individuals with renal impairment). Data from the published articles are summarized in Table 1.[4–12]

The case presented here demonstrates some typical features of Goodpasture's syndrome. They are usually young, male and cigarette smokers, presenting with pulmonary hemorrhage and glomerulonephritis with or without renal dysfunction. Our patient also had a history of exposure to hydrocarbon fumes. However, the minor hematuria and proteinuria were overlooked when he presented to a local hospital. Thus, the renal involvement was not incorporated into the formulation of the differential diagnosis for causes of the intra-alveolar hemorrhage. He was suspected to have pulmonary infection, pulmonary tuberculosis, tumor, or idiopathic pulmonary hemosiderosis. He was treated with antibiotics for 3 weeks for suspected infection, without any improvement, before the detection of anti-GBM antibodies in his sera. This patient's history highlights the importance for physicians to consider the diagnosis of anti-GBM disease in patients with pulmonary hemorrhage, even when, as in this patient, the renal function was normal and the urinalysis revealed minimal abnormalities or no abnormalities (Table 2).

The evidence of anti-GBM antibodies detected in sera or renal tissue is of vital importance in the diagnosis of anti-GBM disease with normal renal function. The circulating antibodies in the current case were demonstrated cautiously by ELISA using purified bovine α(IV)NC1 and recombinant human α3(IV)NC1 as solid-phase antigen, respectively, and were further confirmed by Western blot analysis using purified human α(IV)NC1 as antigen (Figure 3). The deposition of antibodies in renal tissue was demonstrated by linear staining of IgG++ and C3++ along GBM in immunofluorescence assay of renal biopsy (Figure 2). Thus, considering the clinical features of pulmonary hemorrhage and mild proteinuria and hematuria, the diagnosis of anti-GBM disease was confirmed.

### The prevalence of anti-GBM disease with normal kidney function

Patients with anti-GBM disease with normal kidney function are not uncommon. In Peking University First Hospital, the prevalence is approximately 3%.[12] Other studies had found that 15–36%[4–12] of patients with anti-GBM disease have normal kidney function. This variation might be due in part to 'normal' kidney function being defined by levels of serum creatinine, creatinine clearance, or clear urinary sediment. An alternative explanation may be that anti-GBM disease is recognized early, since there is heightened awareness of anti-GBM disease as one potential cause of hemoptysis.[13,14]

We have also speculated that this subgroup of patients with anti-GBM disease with normal kidney function is recognized frequently because of improved immunodiagnostic techniques. Diagnosis of anti-GBM disease is based on the detection of anti-GBM antibodies in serum or in tissue, and a positive serum assay is diagnostic of the disease. The ELISA and radioimmunoassay are the most sensitive and specific methods. Indeed, false-negative results had been reported with serum indirect immunofluorescence assays using frozen human kidney sections as substrate. Therefore, a negative result with indirect immunofluorescence assay does not exclude anti-GBM disease. Furthermore, ELISA and radioimmunoassay are more convenient and amenable to be used as screening tests in the detection of anti-GBM antibodies.

The likelihood of pulmonary involvement is probably increased among those who smoke[15] or have been exposed to organic solvents.[16] The permeability of lung capillaries is increased and thereby enables circulating antibody to reach the alveolar basement membrane. Furthermore, smoking and inhalation of hydrocarbon fume themselves may damage the alveolar basement membrane and thereby induce the formation of antibasement membrane antibodies, and by crossreacting with GBM, cause nephritis and hemorrhage. Linear immunoglobulin deposition along alveolar basement membranes is diagnostic of antibasement membrane disease, especially when lung hemorrhage is the main manifestation. However, a significant incidence of false-negative results of immunofluorescent microscopy has been found with transbronchial biopsy specimens, thus is not a reliable method to exclude anti-GBM disease.[5] This shortcoming leads us to ELISA or radioimmunoassay for anti-GBM antibodies in serum as a method of anti-GBM disease detection. This approach has been suggested in the investigation of alveolar hemorrhage syndromes with or without renal damage, and has been recommended before diagnosing idiopathic pulmonary hemosiderosis.

### The relationship between anti-GBM antibodies and renal function

Earlier data indicate that patients with anti-GBM disease with normal kidney function usually have a lower level of circulating anti-GBM antibodies than those with significant renal impairment.[8,11,17] The titer of anti-GBM antibodies of this patient was 1:400, whereas of patients with classic Goodpasture's syndrome it was approximately 1:1000.[18] To date, the observation of lower levels of circulating anti-GBM antibodies remained the most significant difference between patients with normal and impaired kidney function.[8,11,17] This case also supports the contention that lower levels of circulating anti-GBM antibodies might correlate with better preserved renal function. The correlation between antibody titers and the serum creatinine on diagnosis or the prognosis of renal function has been reported by us and other investigators previously.[12,19,20]

Another mechanism by which anti-GBM antibodies may vary between patients is the physiochemical characteristics of the immunoglobulin present. The subclasses of IgG antibodies might be different between patients. Previous studies

**Table 1 | Findings of patients with anti-GBM disease and normal renal function**

| No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Year reported | 1975 | 1981 | 1981 | 1990 | 1993 | 1993 | 1996 |
| Journal | *Ann Intern Med*[4] | *Clin Nephrol*[8] | *Clin Nephrol*[8] | *Am Rev Resp Dis*[5] | *Am J Nephrol*[9] | *Nephrol Dial Transplant*[6] | *Nephrol Dial Transplant*[10] |
| Age/gender | 18/M | 18/M | 20/M | 20/M | 23/F | 24/M | 22/M |
| Exposure to gasoline fumes | N | Y | Y | N | N | Y | Y |
| Smoke | N | Y | Y | *Y* | Y | N | Y |
| *Clinical features* | | | | | | | |
| Lung | Hemoptysis | Hemoptysis | Hemoptysis | Hemoptysis | Upper respiratory tract infection | N | Hemoptysis |
| Chest radiograph | Diffuse mottled opacity over both lung fields | Intra-alveolar shadowing in both lungs | Widespread fine nodular shadowing in both lungs | Right upper lobe infiltration | None | Bilateral alveolar densities | Bilateral mid- and lower-zone consideration |
| Urinalysis | Normal | Upr 1 g/24 h, $30–100 \times 10^6$ red cells/l | Upr 0.24 g/24 h, less than $1 \times 10^6$ red cells/l | Normal | Upr 2.88 g/24 h, red cells 20–40/HPF | Normal | Microscopic hematuria and proteinuria |
| Hemoglobin | 40 g/l | 43 g/l | 130 g/l | 80 g/l | 146 g/l | 76 g/l | 75 g/l |
| Circulating anti-GBM antibodies | None | (+) | (+) | (−) | (−) | (−) | (+) |
| Other antibodies | ANA (−), RF(−), Coombs' test(−) | Coombs' test (−) | None | ANA (−), RF(−) | ANA (−), ANCA (−) | ANA (−) | ANA (−), ANCA (−) |
| *Biopsy* | | | | | | | |
| IF | Linear IgG deposition along GCW | Linear IgG 3+ and C3 1+ deposition along GCW | Linear IgG deposition along GCW | Linear IgG 4+ deposition along GCW | Linear IgG 3+ deposition along GCW | Linear IgG and C3 deposition along GCW | Linear deposition of IgG in alveoli |
| LM | Mild increase in mesangial prominence | Glomerular swollen and hypercellular, 2/20 glomeruli showed epithelial crescents | Mild segmental increase in mesangial matrix and cellularity | Normal | Mild to diffuse mesangial proliferation, 4/22 glomeruli had cellular crescents | Normal cellularity and uniformly thin capillary loops | None |
| Treatment | P | None | None | P | PE/P/Aza | PE/P/C | PE/P |
| Prognosis | No hemoptysis, renal function and urinalysis remained normal | No hemoptysis, no red cells and a trace of protein in urinalysis, with normal renal function | No hemoptysis, renal function and urinalysis remained normal | No hemoptysis, renal function and urinalysis remained normal | Trace protein and 0–2 red cells/HPF in urinalysis and normal renal function | Chest X-ray was normal, urinalysis and renal function remained normal | No hemoptysis and normal renal function |
| Follow-up | 2 years | 5 years | 4 years | 2 years | 2 years | 8 years | 2 months |

A, Azathioprine; C, cyclophosphamide; F, female; GCW, glomerular capillary wall; GBM, glomerular basement membrane; HPF, high power field; IF, immunofluorescence; LM, light microscopy; M, male; N, no; P, prednisone; PE, plasma exchange; Upr, urine protein.
Data complied from published case reports

have implicated subclasses IgG1 and IgG4 in the majority of cases of Goodpasture's syndrome.[21,22] IgG subclasses of serum anti-GBM antibodies in the current patient, tested by ELISA, revealed a restriction of IgG4 activity. It has been suggested that IgG4 subclass dominance could be explained by chronic antigen stimulation. In the patient reported herein, a possible explanation was the chronic exposure to gasoline and smoking, which might lead to the exposure of the Goodpasture antigen. Additionally, different IgG subclasses have different biological properties; for example, IgG4, unlike IgG1, does not efficiently bind C1q and therefore does not activate the classical pathway of complement. As well, the IgG Fc receptors on mononuclear macrophage poorly bind IgG4. Thus, IgG4 is unlikely to trigger severe inflammatory damage in the glomeruli. We have observed previously that anti-GBM antibodies in patients with mild renal dysfunction (serum creatinine $< 300\ \mu$mol/l) were predominantly of IgG4 subclasses (75%),[23] which supports the speculation that IgG subclasses of anti-GBM antibodies may be associated with different clinical presentations and disease progression.

**Table 2 | A summary of the clinical features, treatment, and prognosis of patients with anti-GBM disease and normal renal function[4–12]**

| No. | N | % (N=13) |
|---|---|---|
| Male/female | 10:3 | |
| Median age, years | 22 (18–79) | |
| Exposure to gasoline fumes | 4 | 30.8 |
| Smoke | 6 | 46.2 |
| Macroscopic hematuria | 3 | 23.1 |
| Microhematuria | 7 | 53.8 |
| Proteinuria | 10 | 76.9 |
| BP > 140/90 mm Hg | 0 | 0 |
| Hemoptysis | 8 | 61.5 |
| Malaise, fever, LOW | 4 | 30.8 |
| Hb < 90 g/l | 7 | 53.8 |
| Chest radiograph abnormality | 8 | 61.5 |
| Circulating anti-GBM antibodies | 6 | 50.0 (N=12) |
| *Renal biopsy* | | |
| Linear IgG deposition along GCW in IF | 13 | 100 |
| Normal | 3 | 25.0 (N=12) |
| Proliferation in mesangium | 9 | 75.0 (N=12) |
| Crescents < 50% | 2 | 16.7 (N=12) |
| Crescents > 50% | 0 | 0 |
| *Treatment* | | |
| PE | 5 | 38.5 |
| P | 10 | 76.9 |
| C or A | 6 | 46.2 |
| No treatment | 3 | 23.1 |
| *Prognosis* | | |
| Hematuria | 4 | 30.8 |
| Proteinuria | 7 | 53.8 |
| Scr↑/Ccr↓ | 0 | 0 |
| Follow-up, median months | 48 (2–96) | |

A, Azathioprine; BP, blood pressure; C, cyclophosphamide; Ccr, creatinine clearance; GCW, glomerular capillary wall; GBM, glomerular basement membrane; Hb, hemoglobin; IF, immunofluorescence; LOW, loss of weight; P, prednisone; PE, plasma exchange; Scr, serum creatinine.

**Table 3 | The difference between natural and disease-associated anti-GBM antibodies[18]**

| | Natural anti-GBM antibodies | Antibodies in the current case | Disease-associated anti-GBM antibodies |
|---|---|---|---|
| Percentage of IgG | 0.5 | N | 1 |
| Titer | 1:60 | 1:400 | 1:1000 |
| IgG subclasses | IgG2 and IgG4 | IgG4 | Mainly IgG1 and IgG4 |
| *AK* | $9.09 \times 10^7\ M^{-1}$ | $4.0 \times 10^6\ M^{-1}$ | $3.26 \times 10^8\ M^{-1}$ |

GBM, glomerular basement membrane; N, not known.
aK, affinity constant of anti-GBM antibodies, measured as the reciprocal value of molar concentration of α(IV)NC1 needed for 50% inhibition of the binding capacity of the antibodies.

High affinity of the antibodies is another factor that could contribute to the fulminant nature and treatment resistance of anti-GBM disease.[24] The functional affinity of this patient's antibodies was detected by antigen-inhibition ELISA as described previously.[25,26] The functional affinity constant (aK) was measured as the reciprocal value of molar concentration of α(IV)NC1 needed for 50% inhibition of the binding capacity of the antibodies.[27] The aK in this case was $4.0 \times 10^6\ M^{-1}$, much lower than that of patients with classic anti-GBM disease (aK $3.26 \times 10^8\ M^{-1}$).[18] Our previous study has indicated that the functional affinity of anti-GBM antibody is closely associated with the percentage of glomerular crescent formation in patients with anti-GBM disease.[26] Therefore, the low affinity of anti-GBM antibodies of this patient could be another explanation for the less severe involvement of the kidney.

Other investigators have suggested the possibility that the presence of antibodies to epitopes other than α3(IV)NC1, that is, α1(IV)NC1 and α4(IV)NC1 found in a minority of cases (15%), might lead to differing presentations of anti-GBM disease.[19,28] It does not seem to be of relevance to the case presented here, as antibodies in this patient reacted to α3(IV)NC1, exclusively.

The recent detection of natural autoantibodies against GBM in normal human serum has attracted more attention to this subset of patients with anti-GBM disease and normal renal function. Comparing the characteristics of anti-GBM antibodies in this case with those in healthy persons and in patients with anti-GBM disease (Table 3),[18] we observed that antibodies in this patient appeared to be more like those in healthy persons. The long-term follow-up of patients similar to the case reported herein revealed a good prognosis for renal function even without treatment. This observation taken together with the differences in the pattern of antibodies between these patients and those with classic anti-GBM disease tends to not support the suggestion that these patients might represent an earlier stage of classic anti-GBM disease. We speculate that this group of patients may be a unique subtype of anti-GBM disease. The elucidation of humoral and cellular immunity in these patients could be of vital importance in investigations of the pathogenesis of anti-GBM disease.

## The treatment and prognosis of anti-GBM disease with normal renal function

Individuals with anti-GBM disease and renal impairment or pulmonary hemorrhage are generally treated with plasmapheresis and immunosuppression to preserve any residual renal function and to control bleeding; following a course of treatment, antibodies disappear and rarely recur. Patients with anti-GBM disease and normal renal function have a good prognosis when treated aggressively; indeed, treatment is indicated when there is hemoptysis[5,7] or when renal histology is changed.[11] Although the use of less aggressive strategies or supportive treatment has only occasionally been associated with spontaneous recovery and persistently normal renal function,[5,10] this approach is not recommended.

## Conclusion

Anti-GBM disease with normal renal function is not rare. The key point for diagnosis lies on the physicians to consider

this disease when the patients present with lung hemorrhage or moderate to severe anemia, and when the urinalysis revealed minimal abnormalities or even no abnormalities. Under the aggressive treatment, a good prognosis of maintaining normal renal function can be expected, in spite of mild proteinuria or hematuria may leave in some patients.

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